Sudden cardiac death accounts for approximately 300,000 deaths annually in the U.S., and most of these are secondary to ventricular tachycardia (VT) and fibrillation in patients with coronary artery disease. Most patients with cardiac death die before reaching the hospital, which brought about a tremendous amount of research focused at identifying patients at high risk. Several trials were initiated to test the effectiveness of various therapeutic measures in these high-risk patients. A history of myocardial infarction, depressed left ventricular function and nonsustained VT have all been identified as independent risk factors for future arrhythmic death. Similarly, patients with a history of sustained VT or a history of sudden cardiac death are a high-risk group and should be aggressively evaluated and treated. The purpose of this article is to discuss risk stratification and primary prevention of sustained ventricular arrhythmias. We also review the recent secondary prevention trials and discuss the options available in the management of patients with sustained ventricular arrhythmias. (J Am Coll Cardiol 1999;34:621–30) © 1999 by the American College of Cardiology

Sudden cardiac death, defined as instantaneous death within 1 h of an abrupt change in clinical status, accounts for approximately 300,000 deaths in the U.S. annually (1). Most sudden deaths are due to ventricular tachycardia (VT) or ventricular fibrillation (VF). Although some sudden death victims have no overt evidence of cardiovascular disease, patients with existing heart disease are at higher risk. Many cardiac diseases may increase the risk of ventricular arrhythmias and sudden death, but acute ischemia and prior myocardial infarctions (MIs) are by far the most common, with over 50% of all sudden cardiac deaths occurring in patients with coronary artery disease (2). This review addresses the management of ventricular arrhythmias in patients having coronary artery disease, with an emphasis on some of the latest clinical trials. In the first section, we will discuss risk stratification and primary prevention of sustained ventricular arrhythmias, and in the second section, we summarize the options available in the management of sustained ventricular arrhythmias with emphasis on the recent secondary prevention trials.

RISK STRATIFICATION AND PRIMARY PREVENTION OF SUSTAINED VENTRICULAR ARRHYTHMIAS

Most sudden cardiac deaths are the result of sustained ventricular tachyarrhythmias, but unfortunately, most patients with sudden death die before reaching the hospital. Because the number of patients surviving to hospitalization with sustained ventricular arrhythmias represent a fraction of the patients who may be at risk for an arrhythmic event, a tremendous amount of research has focused on developing risk stratification methods to identify the patient at highest risk. A number of trials have been performed to test the effectiveness of various prophylactic treatment strategies for high-risk patients. Because patients with coronary artery disease represent most high-risk patients, many large clinical trials have excluded other patient groups. In the section that follows, we summarize the data for risk stratification and primary prevention of sustained ventricular arrhythmias in patients with coronary artery disease.

Risk stratification. Many articles published before the widespread use of thrombolytic therapy and beta-adrenergic blocking agents, describe risk factors for sudden death in patients with previous MIs. The risk of sudden death after a MI is approximately 5% per year for at least three to five years after an infarction. The risk is proportional to the degree of left ventricular dysfunction, with a left ventricular ejection fraction below 40% the best predictor of an adverse long-term outcome (3–7). Asymptomatic ventricular arrhythmias, including premature ventricular contractions (PVCs) and nonsustained VT (three beats to 30 s of VT), are also valuable for predicting outcome in patients with coronary artery disease. Isolated ventricular ectopy is common after MI, and up to 80% of patients will have some ectopy present on a 24-h ambulatory (Holter) monitor (8). A report of the 1,640 patients in the placebo arm of the Beta-Blocker Heart Attack Trial (B-HAT) who were not
SAECG is used in patients with known left ventricular dysfunction, the sensitivity, specificity and positive predictive value are all enhanced. Patients with left ventricular ejection fractions <40% and a positive SAECG plus frequent ectopy or nonsustained VT on Holter are at very high risk for suffering arrhythmic events during a two-year follow up (45% to 50%) (17). Thus, the results of ambulatory monitoring and signal-averaged electrocardiograms are perhaps best interpreted in combination with a determination of left ventricular function to identify those patients at highest risk of arrhythmic events or sudden death after MI (18). Further evaluation of this approach is necessary, and will be available after analysis of the Multicenter Unsustained Tachycardia Trial (MUSTT) study (see following section).

Evidence to date has shown that signal-averaged electrocardiography and Holter monitoring combined with a determination of ejection fraction have high negative predictive value but relatively poor positive predictive value (19). Because of low positive predictive value, the results of these noninvasive tests frequently cause referral for invasive electrophysiologic study using programmed electrical stimulation. Programmed stimulation is both a sensitive and specific technique for inducing monomorphic VT in patients with coronary artery disease; such patients who present with this arrhythmia have the VT reproduced in over 90% of cases (20). It has also been used to risk stratify patients after MI, with sustained VT induced in 21% to 25% of all patients (21–23). Use of a full programmed electrical stimulation protocol with three extrastimuli increases inducibility rates up to 45% (24). Patients without inducible ventricular arrhythmias have event-free survival rates ranging from 88% to 96%, regardless of the presence of left ventricular dysfunction, nonsustained ventricular arrhythmias or a positive signal averaged electrocardiogram (25). This demonstrates the excellent specificity and negative predictive value of programmed electrical stimulation in

treated with beta-blockers identified frequent ventricular ectopy (>10 PVCs/h) and nonsustained VT as independent risk factors for sudden death (8). Many other studies have confirmed that nonsustained VT and frequent, multiple or complex ventricular extrasystoles detected by ambulatory monitoring are significant, independent risk factors for sudden death (3). In general, more frequent or complex ventricular ectopy is associated with a worse prognosis. Most studies indicate that the risk of sudden death begins to rise if greater than three PVCs/h are present, and rises sharply if >10 PVCs/h are present (9–11). Nonsustained VT has also been shown to be a predictor of sudden death, particularly in patients with left ventricular dysfunction (6). Because nonsustained ventricular arrhythmias and left ventricular dysfunction are independent risk factors, patients with both have the worst long-term survival (odds ratio for sudden death 2.35 to 4.7) (Fig. 1) (6,7,12).

Signal-averaged electrocardiography (SAECG) is a commonly used noninvasive method for risk stratification. An abnormal signal average electrocardiogram correlates with the presence of both clinical and laboratory-induced VT in patients presenting with sustained VT. The SAECG has also been used to risk stratify patients after MI, and a negative predictive value of ≥90% has been demonstrated. However, the positive predictive value for death or an arrhythmic event is only 16% to 31% (13–16). When SAECG is used in patients with known left ventricular
Sotalol was first tested in patients with a history of MI in 1982. In this trial (28), patients began receiving either \( d,l \)-sotalol 320 mg per day or placebo on day 5 to 14 post-MI and were followed for one year. Patients treated with sotalol had an 18% reduction in total mortality (7.3% in the sotalol group vs. 8.9% in the placebo group, relative risk = 0.81). This reduction in mortality rate, however, may have been due solely to the beta-blocking activity of the drug. The Survival with Oral \( d \)-Sotalol (SWORD) trial was designed to test whether the pure \( d \)-stereoisomer of sotalol, which retains the class III potassium-channel blocking activity but lacks beta-blocking activity, would prolong survival in patients with depressed left ventricular function after MI. The trial was terminated prematurely due to excess mortality in the treatment group, which appeared to be secondary to enhanced arrhythmic death. The authors concluded that \( d \)-sotalol did not reduce mortality and may be associated with increased mortality (29). Of note, mortality was highest in low-risk patients and minimal in high-risk patients. The increase in mortality in the low-risk group was probably secondary to drug proarrhythmia. Both sotalol trials are summarized in Table 1.

Several studies have examined the benefit of amiodarone for patients with prior MI. The Basel Antiarrhythmic Study of Infarct Survival (BASIS) randomized post-MI patients to one of the following treatments for one year: 1) individualized antiarrhythmic drugs, starting with class IA agents; 2) low-dose amiodarone, or 3) no antiarrhythmic therapy (30). End points were total mortality and arrhythmic events. Using an intention-to-treat analysis, patients receiving amiodarone had less arrhythmic events and a higher probability of survival (31,32). The Polish Amiodarone Pilot Study was designed to test the effect of amiodarone on mortality, ventricular arrhythmias and clinical complications in post-MI patients unable to take beta-blocking drugs (33). After a one-year follow-up, patients treated with amiodarone had a nonsignificant improvement in total survival compared with patients receiving placebo, although there was a statistically significant difference in cardiac mortality rates between the two groups. The frequency of ventricular arrhythmias was significantly reduced by amiodarone (33). In the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT) pilot study (34), 77 post-MI patients with 10 or more PVCs/h were randomized to amiodarone versus placebo. At the 2-year follow up, the incidence of arrhythmic death or resuscitated VF was 6% in the amiodarone group and 14% in the placebo group. Similarly, the all-cause mortality rate was 10% in the amiodarone group versus 21% in the placebo group. The encouraging results of these early studies led to the design of two large trials to test the benefit of amiodarone in post-MI patients: the European Myocardial Infarct Amiodarone Trial (EMIAT), and the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT).

The objective of EMIAT was to assess the effect of amiodarone on all-cause mortality and arrhythmic death in...
<table>
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<tr>
<th>Coronary artery disease</th>
<th>n</th>
<th>CAD</th>
<th>Low EF</th>
<th>PVCs</th>
<th>NSVT</th>
<th>Therapy</th>
<th>Follow-up (months)</th>
<th>Findings</th>
<th>Conclusions</th>
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<td>Class 1C:</td>
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<td>CAST (1989)</td>
<td>1498</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>Encainide or Flecainide vs. Placebo</td>
<td>10</td>
<td>7.7% mortality (treatment) vs. 3.0% (placebo)</td>
<td>Terminated prematurely due to excess mortality in treatment group</td>
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<td>Amiodarone:</td>
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<td>BASIS (1990)</td>
<td>312</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>Amio vs. Mexiletine or Quinidine vs. no therapy</td>
<td>72</td>
<td>5% mortality (amio) vs. 10% (Class 1) vs. 13% (placebo)</td>
<td>Amio improved survival, nonsignificant trend with Holter-guided PVC suppression</td>
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<td>POLISH (1992)</td>
<td>613</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>Amio vs. Placebo</td>
<td>12</td>
<td>6.9% mortality (amio) vs. 10.7%, not significant</td>
<td>Amio reduced arrhythmic death rate without affecting total survival</td>
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<td>EMIAT (1997)</td>
<td>1486</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>Amio vs. Placebo</td>
<td>21</td>
<td>7.2% mortality (both groups), 35% RR in arrhythmic death</td>
<td>Amio reduced arrhythmic death rate without affecting total survival</td>
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<td>CAMIAT (1997)</td>
<td>1202</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>Amio vs. Placebo</td>
<td>21</td>
<td>3.3% VF/SCD (amio) vs. 6.0% (placebo), RR 21.2%</td>
<td>Prophylactic amio improved survival for frequent/repetitive PVCs</td>
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<td>MADITII (1996)</td>
<td>196</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>ICD vs. conventional therapy</td>
<td>27</td>
<td>15.7% mortality (ICD) vs. 38.6% (placebo), RR 46%</td>
<td>Terminated prematurely because of significant ICD benefit</td>
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<td>CABG-PATCH (1997)</td>
<td>900</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>ICD vs. no ICD</td>
<td>36</td>
<td>No difference in all-cause mortality</td>
<td>All patients had abnormal SAECG; no benefit of prophylactic ICD</td>
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<td>MUSTT (incomplete)</td>
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<td>EP-guided or ICD vs. no therapy</td>
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<td>Sotalol:</td>
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<td>Julian et al. (1982)</td>
<td>1456</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>d,l-Sotalol vs. Placebo</td>
<td>12</td>
<td>7.3% mortality (Sotalol) vs. 8.9% (placebo), RR 18%</td>
<td>d,l-Sotalol may reduce mortality by up to 25%</td>
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<td>3121</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>d,l-Sotalol vs. Placebo</td>
<td>5</td>
<td>5.0% mortality (Sotalol) vs. 3.1% (placebo)</td>
<td>Trial terminated due to excess mortality in the treatment group</td>
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<td>CHF amiodarone trials</td>
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<tr>
<td>GESICA (1994)</td>
<td>516</td>
<td>~1/3</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>Amio vs. standard therapy</td>
<td>24</td>
<td>33.5% mortality (amio) vs. 41.4% (control), RR 28%</td>
<td>Amio improved survival in symptomatic heart failure</td>
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<td>CHF-STAT (1995)</td>
<td>674</td>
<td>~2/3</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>Amio vs. placebo</td>
<td>45</td>
<td>30.6% mortality (amio) vs. 29.2% (placebo)</td>
<td>No survival benefit with amio; trend to improved survival in DCM subgroup</td>
</tr>
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</table>

+ = Inclusion criterion; − = Not inclusion criterion; amio = amiodarone; CAD = coronary artery disease; CHF = congestive heart failure; DCM = dilated cardiomyopathy; EF = ejection fraction; ICD = implantable cardioverter-defibrillator; NSVT = nonsustained ventricular tachycardia; PVCs = premature ventricular contractions; RR = risk reduction; SCD = sudden cardiac death; VF = ventricular fibrillation. See text for clinical trial abbreviations.
patients with left ventricular dysfunction 5 to 21 days after MI. No effect on all-cause mortality was demonstrated, and the investigators concluded that despite the reduction in arrhythmic death rate, routine use of prophylactic amiodarone after MI was not warranted because of the lack of demonstrable effect on total mortality (35). The CAMIAT trial was designed to test the effect of amiodarone on the risk of arrhythmic death or resuscitated VF among survivors of MI with frequent or repetitive PVCs or nonsustained VT. In this trial, amiodarone reduced the incidence of arrhythmic death and resuscitated VF (38.2%, p = 0.029). These reductions were greatest among patients with congestive heart failure (CHF) (36). A limitation of this study was the lack of assessment of left ventricular dysfunction, a known predictor of arrhythmic events and mortality in post-MI patients. Both trials have demonstrated the safety of amiodarone use in post-MI patients, and that its potential benefit is best seen in high-risk patients taking beta-blockers. A summary of all the post-MI amiodarone trials is provided in Table 1.

The GESICA (Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina) and CHF-STAT (Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure) trials assessed the effect of amiodarone on total mortality in patients with left ventricular dysfunction regardless of the etiology (See Table 1). The GESICA trial compared low-dose amiodarone with standard therapy in patients with severe CHF who did not have symptomatic ventricular arrhythmias. The mortality rate in the treatment group was 33.5% compared with 41.4% in the control group, and was independent of the presence of nonsustained VT at baseline (37). The investigators concluded that amiodarone was beneficial to patients with CHF. The CHF-STAT trial evaluated amiodarone versus placebo in 674 patients with CHF, cardiac enlargement, a left ventricular ejection fraction of 40% or less and 10 or more premature ventricular contractions per hour. The cause of heart failure was ischemic in 71% of patients. Although amiodarone reduced the frequency of PVCs and nonsustained VT, it did not reduce the incidence of sudden death or prolong survival. Subgroup analysis showed a trend toward improvement in survival in patients with nonischemic cardiomyopathy, but the difference did not reach statistical significance. Moreover, in the subgroup with nonsustained VT before randomization and in the subgroup with suppression of ventricular ectopy by amiodarone, no survival benefit was apparent (38). The disparity between GESICA and CHF-STAT could have been due to differences in the patient populations. In the GESICA trial, 61% of the patients had nonischemic cardiomyopathies, compared with 29% in CHF-STAT, suggesting that prophylactic amiodarone may be more beneficial to patients with nonischemic cardiomyopathy.

The Multicenter Automatic Defibrillator Implantation Trial (MADIT) tested the hypothesis that prophylactic implantation of a cardioverter-defibrillator (ICD) in high-risk patients with nonsustained VT, coronary artery disease and a positive electrophysiologic study would improve survival when compared with conventional medical therapy. During electrophysiologic testing, sustained VT or fibrillation had to be reproducibly induced with programmed stimulation and not suppressed with intravenous procainamide. Patients were then randomized to receive either "conventional antiarrhythmic therapy" or an ICD. The safety and monitoring committee terminated the study prematurely because of excess mortality with conventional antiarrhythmic therapy (See Table 1). Many critics argue that this trial was not a fair comparison between antiarrhythmic drug therapy and ICD therapy for the following reasons: 1) Suppression with procainamide was considered an exclusion criterion, thus eliminating patients that may have done well on other conventional drugs such as amiodarone; 2) Twenty-three percent of patients randomized to conventional therapy were on no antiarrhythmic medications and 44% of the ICD group were taking an antiarrhythmic agent, giving the impression that this was almost a comparison between ICD combined with antiarrhythmic therapy and no therapy at all; 3) Beta-blockers were used in 27% of patients with an ICD implant and only in 5% of patients receiving conventional therapy; 4) Conventional drug therapy was not EP guided. Despite these limitations, the Food and Drug Administration recently approved the implantation of ICD in MADIT-like patients. In the authors' opinion, patients with coronary artery disease, left ventricular dysfunction and nonsustained VT should undergo programmed electrical stimulation, and if inducible, receive an ICD implant (39).

The Coronary Artery Bypass Graft (CABG) Patch Trial was based on the hypothesis that ICD implantation at the time of CABG surgery would improve survival in 900 patients with depressed ejection fractions and positive preoperative signal-averaged electrocardiograms. During an average follow-up of 32 months, 101 patients with ICDs died, compared with 95 from the control group. This difference was not significant, and the authors concluded that prophylactic ICD therapy was of no benefit in this population (see Table 1) (40). The findings in this trial are clearly different from the MADIT, and we think this is best explained by the following: 1) All CABG-PATCH patients underwent revascularization, which could have altered the electrical milieu responsible for future arrhythmic events, and 2) signal-average electrocardiogram is probably a poor marker of arrhythmic events in comparison with spontaneously or induced VT.

Antiarrhythmic therapy guided by invasive electrophysiologic testing has historically been used to treat patients with nonsustained ventricular arrhythmias after MI who have inducible VT at electrophysiologic study, but this approach has never been tested systematically. It has been suggested that a favorable response to antiarrhythmic therapy simply identifies a lower risk population, and no direct benefit is gained by treatment with antiarrhythmic drugs.
The Multicenter Unsustained Tachycardia Trial (now in follow-up) will address this issue and is based on the following two hypotheses. First, EP-guided antiarrhythmic therapy can reduce sudden death and overall mortality in survivors of acute MIs; and second, the SAEGC can identify the highest risk patients (41). The entry criteria required that patients have coronary artery disease, a left ventricular ejection fraction of 40% or less and nonsustained VT. All candidates underwent SAEGC and baseline electrophysiology study. Patients with no inducible arrhythmia are being followed without antiarrhythmic therapy. Patients with inducible VT were randomized to receive either no therapy or antiarrhythmic therapy guided by serial electrophysiologic testing (or an ICD if VT remained inducible and hemodynamically significant despite drug treatment). Initially, up to three drug tests were performed before implantation of a defibrillator or initiation of amiodarone therapy, but this was reduced to a single drug test before completion of enrollment. The first drug choice was randomly assigned as class IA (quinidine, procainamide or disopyramide), class IC (propafenone) or class III (sotalol) (41). Patients who remained inducible on the initial antiarrhythmic drug usually received either amiodarone or an ICD, although many different drugs and drug combinations were specified as treatment options in the protocol. Enrollment was completed for MUSTT in 1997, and follow-up continues. Of note, preliminary data show that the cycle length, frequency and duration of nonsustained VT do not predict induction of VT or VF by programmed stimulation (42).

Summary of primary prevention trials. Several recommendations can be made based on the results of these primary prevention trials in patients with coronary artery disease. First, the use of class I antiarrhythmic drugs to suppress frequent ventricular ectopy is associated with increased mortality and is therefore contraindicated. Second, the one large trial of d-Sotalol (SWORD) was terminated early because of excess mortality, and thus the empiric use of d-Sotalol cannot be recommended. Third, high-risk patients with low ejection fractions, nonsustained VT and inducible VT not suppressed by procainamide appear to benefit from ICD therapy. Fourth, the use of amiodarone for primary prevention of sudden death in patients with either ischemic or nonischemic cardiomyopathies is not associated with an adverse outcome, but likewise, has not been proved to confer a survival benefit. A recent meta-analysis of all 13 randomized primary prevention trials using amiodarone reported a 13% overall reduction in total mortality and a 29% reduction in arrhythmic death. The authors acknowledged the limitations of meta-analyses, but suggested that amiodarone was unlikely to be pro-arrhythmic, and that in high-risk patients, amiodarone use was justified (43).

In summary, it is the authors’ opinion that survivors of an MI should have an assessment of ejection fraction, and if the ejection fraction is reduced, a 24-h Holter monitor no earlier than 4 to 5 days after the infarction. We chose Holter monitoring because the results of the MADIT and CABG-PATCH trials suggest that spontaneous VT is a better marker than SAEGC for predicting future arrhythmic events. Definite recommendations for the clinical use of signal-averaged electrocardiogram should await the publication of the MUSTT results. Patients with low ejection fractions and nonsustained VT may be treated empirically with amiodarone, recognizing that amiodarone therapy for this patient population is still controversial. Referral for an electrophysiology study for further risk stratification and possible ICD therapy is a reasonable approach in these patients. In our opinion, patients with inducible VT should have an ICD implanted. The results of the MUSTT trial will shed some light on the role of EP-guided therapy and how it compares with ICD therapy or no therapy at all in these high-risk patients.

Therapy Options for Patients with Ventricular Arrhythmias

Patients who present with sustained VT, sudden cardiac death or syncope in the setting of significant structural heart disease are generally a high-risk group, and little controversy exists that these patients should be aggressively evaluated and treated. The results of the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial (described in the next section), as well as the results of many smaller secondary prevention trials, suggest that the use of ICDs can decrease the risk of sudden death even when compared with treatment with class III drugs such as amiodarone. For this reason, antiarrhythmic drug therapy guided by serial electrophysiologic testing or serial holter monitors is used less often now by electrophysiologists in clinical practice and is usually reserved for patients with refractory arrhythmias leading to frequent defibrillator shocks.

Catheter ablation techniques may also provide a cure for VT patients in selected cases. In bundle branch reentry tachycardia, where the tachycardia is due to macroreentry within the His Purkinje system, radiofrequency ablation of the right bundle branch is curative (44). This type of VT usually has a left bundle branch block/superior axis morphology and occurs in patients with dilated cardiomyopathy. Patients with “normal heart” idiopathic sustained VT also enjoy great success rates, with up to 90% of patients cured (45,46). In selected cases of sustained, monomorphic VT occurring in the setting of coronary artery disease, radiofrequency ablation can be successful in up to 73% of patients (47). This type of treatment; however, remains an adjunctive therapy in patients with ischemic VT.

Surgical resection represents a potential cure for VT in well-selected cases, but is associated with substantial mortality (up to 20%) (48,49). Surgical resection for VT has been largely replaced by ICD therapy (see below), but remains an option at selected centers, especially when...
surgical resection of a left ventricular aneurysm is also indicated due to hemodynamic compromise.

**Secondary prevention trials.** A number of studies published before the widespread use of ICDs showed that suppression of inducible ventricular arrhythmias during treatment with an antiarrhythmic drug was associated with improved survival (50). Of the patients who were rendered noninducible with antiarrhythmic therapy, arrhythmic event rates ranged from 11% to 31%. Conversely, arrhythmic event rates range from 35% to 88% for patients with inducible VT not suppressed with EP-guided therapy who subsequently received empiric antiarrhythmic drug treatment (Fig. 3) (21–24,41). Nearly all clinical arrhythmia events occurred in patients with inducible arrhythmias and left ventricular ejection fractions below 40%. Some investigators have questioned whether the survival benefit is derived from the antiarrhythmic drug, or whether the response to antiarrhythmic drugs has simply identified a population already at lower risk (24). Programmed stimulation may also be used to determine whether antitachycardia pacing (as delivered by an ICD) will be an effective therapeutic modality.

For several years, experts debated the relative merit of Holter-guided versus EP-guided antiarrhythmic drug therapy for patients with ventricular arrhythmias or for cardiac arrest survivors. Mitchell et al. (51) demonstrated a statistical benefit of EP-guided therapy, although the numbers were relatively small (57 patients). The noninvasive approach required fewer drug trials and fewer hospital days, but the two-year actuarial probability of recurrence was 0.50 ± 0.10 for the noninvasive technique versus only the 0.20 ± 0.08 for the EP-guided approach (p = 0.02). In contrast, Graboys et al. (52) showed that patients with sustained arrhythmias treated with antiarrhythmic drugs had improved survival if ventricular ectopy was reduced during therapy as assessed by 24-h ambulatory monitoring.

The relative advantage of invasive over noninvasive techniques for predicting antiarrhythmic drug success became less clear after the publication of the Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) trial (53). ESVEM included 486 patients who had been resuscitated from cardiac arrest or who had documented sustained VT or syncpe. In addition, inducible VT at electrophysiology study and an average of 10 or more PVCs per hour on Holter monitor were required for enrollment. These patients were randomized to EP-guided therapy or Holter-guided therapy. No significant difference in survival between the two groups occurred over six years, although an acceptable response to medication occurred more frequently in the patients treated with Holter-guided therapy. Of the seven drugs used in ESVEM (imipramine, mexiletine pimelol, procainamide, propafenone, quinidine and sotalol), sotalol was more effective than the other antiarrhythmic drugs in preventing death or recurrence of arrhythmias, regardless of the method of therapy guidance used (54). The ESVEM results should be interpreted with caution. First, the arrhythmia recurrence rate was 50% in both groups at two years, suggesting that neither method for serial testing was very effective in this patient population. Second, both frequent PVCs and inducible VT had to be present for enrollment, which limits the results of this trial to only a fraction of patients with sustained VT or VF. Third, only 22% of patients enrolled had a history of true cardiac arrest, and neither amiodarone nor implantable defibrillators were used in the trial (53).

The debate regarding EP-guided antiarrhythmic drug therapy continued with the publication of the CASCADE study (Cardiac Arrest in Seattle: Conventional Versus Amiodarone Drug Evaluation). The CASCADE compared conventional drug therapy versus amiodarone, randomly assigning outpatient cardiac arrest patients to either empiric amiodarone therapy or treatment with other antiarrhythmic drugs (including class I agents) guided by electrophysiology testing, Holter recording or both (55). The results of CASCADE are somewhat difficult to interpret, because placement of an ICD became standard in all groups in the middle of the trial. However, patients treated with empiric amiodarone had improved survival free of cardiac death, resuscitated cardiac arrest or syncopal episode with ICD shock. Steinbeck et al. (56) compared EP-guided antiarrhythmic drug therapy with beta-blocker therapy in patients with symptomatic, sustained ventricular tachyarrhythmia. Patients with inducible arrhythmia were randomly assigned to receive either EP-guided drug therapy with serial testing or empiric treatment with metoprolol. The incidence of sudden death and symptomatic arrhythmia after two years was similar in both groups. The authors concluded that EP-guided therapy did not improve the overall outcome of patients with sustained ventricular arrhythmias. This conclusion should be interpreted with caution because 52% of patients assigned to EP-guided therapy remained inducible despite testing and were discharged home on antiarrhythmic drug therapy. Recurrent arrhythmia and sudden death was
highest in this group compared with those who became noninducible. If patients with persistently inducible VT had received ICD therapy, the outcome in the EP-guided group would have probably been different.

Until the late 1980s, antiarrhythmic drug therapy was the only option for patients with malignant ventricular arrhythmias (see antiarrhythmic drug therapy section above), but evidence is accumulating that ICDs substantially improve survival in many different patient populations. Data from case-controlled and historical-controlled studies show clear evidence of reduction in sudden cardiac death, although overall mortality changes have been difficult to demonstrate. Certain high-risk groups (such as patients with low ejection fractions) may benefit more than others. One study of cardiac arrest survivors with impaired left ventricular function demonstrated that ICD therapy improved survival compared with conventional therapy from 82.1% to 94.3% at 1 year and 45.3% to 69.3% at 5 years (57). Another study estimated that the ICD improved survival from 72% to 89% at one year and from 49% to 65% at three years (58). Despite these reports of improved survival, concern was raised that overall mortality (as opposed to sudden cardiac death mortality) was not substantially changed by ICD therapy (59,60). In view of these doubts, and the substantial cost of ICD therapy, the National Institutes of Health sponsored the AVID trial. AVID was designed to determine whether placement of an ICD or antiarrhythmic drug therapy resulted in longer survival in patients with life-threatening ventricular arrhythmias. The entry criteria for randomization in AVID included resuscitated VF or VT, although patients with VT were required to have syncope or a left ventricular ejection fraction of ≤40% with hypotension or angina. Coronary artery disease was not an inclusion criterion. Patients were randomized to placement of an ICD or to antiarrhythmic therapy. In the antiarrhythmic therapy arm, patients with any contraindication to sotalol were treated with amiodarone. The remaining patients were randomized to sotalol (EP or Holter-guided) versus amiodarone. At discharge, only 13 patients (2.6%) had adequate arrhythmia suppression with sotalol and remained on the drug. The study was terminated prematurely because of a 26% to 31% reduction in mortality over 1 to 3 years with ICD therapy (61).

The Cardiac Arrest Study-Hamburg (CASH) trial included sudden death patients with documented VT or VF and was designed to compare ICD therapy with treatment with antiarrhythmic drugs (unpublished results). Patients were randomized to receive an ICD, propafenone, metoprolol or amiodarone. The propafenone arm was terminated early because of excess mortality compared with ICDs (29% vs. 11% at one year) (62). At two years, the mortality rate for patients with an ICD was 12.1% compared with 19.6% for antiarrhythmic drugs (combined amiodarone and metoprolol groups). The difference was statistically significant, but because of statistical corrections for multiple comparisons, differences between mortality in the ICD group versus the individual drug groups were not significant. Of note, mor-
tality rates in the amiodarone group and the metoprolol group were identical. In the Canadian Implantable Defibrillator Study (CIDS), patients with VF, cardiac arrest or sustained VT were randomized to ICD versus amiodarone therapy. The primary end point was all-cause mortality. Preliminary results, presented recently, showed a modest reduction of almost 20% with ICD therapy that did not reach statistical significance. Both therapies were well tolerated. A summary of the secondary prevention trials is provided in Table 2.

Although the results of the secondary prevention trials indicate that ICD therapy improves survival in patients with sustained ventricular arrhythmia, it is our opinion that EP-guided therapy remains an acceptable treatment option in certain cases. In patients with sustained VT not associated with syncpe and a left ventricular ejection fraction >40%, EP-guided therapy is a reasonable approach because those patients do not strictly meet the AVID inclusion criteria, and their risk of having a hemodynamically unstable ventricular arrhythmia is low. Similarly, in AVID-like patients who do not wish to have an ICD implanted, amiodarone therapy with serial EP testing may be offered. EP-guided therapy with amiodarone has not yet been compared with ICD therapy in this high-risk population. In our opinion, patients with inducible VT suppressed with amiodarone therapy are likely to have a good prognosis because historically, noninducibility with drug therapy has been associated with a good outcome. However, unless contraindicated, it is our recommendation to proceed with ICD therapy in patients who could have been eligible for entry in the AVID trial.

Conclusions. The treatment of ventricular arrhythmias remains a challenge. A rational approach to patients with ventricular arrhythmias or at risk for them must take into account the predictive value of various risk stratification algorithms. The lessons taught by the CAST trial should be kept in mind: that antiarrhythmic drugs are potentially proarrhythmic and that drug treatment of ventricular arrhythmias may in fact directly harm the patient if undertaken without knowledge of the risks and benefits of the drugs. The implantable defibrillator has revolutionized modern electrophysiology, and the survival benefits of ICD therapy is at last being verified in prospective multicenter studies. Randomized trials have shed substantial light on proper treatment of patients with ventricular arrhythmias, and will continue to shape the way we care for patients at high risk for VT and VF.

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